INTERVIEW SUMMARY

The below summary relates to telephone conversations between Examiner Bruce Hissong and the undersigned representative, Mrs. Valerie Neymeyer-Tynkov, on March 3, 2010, and between Examiner Hissong, Supervisory Examiner Gary Nickol, and Mrs. Neymeyer-Tynkov on May 7, 2010. During both conversations, the Office Action issued October 27, 2009, the Amendment filed February 15, 2010 and claims 54, 55, 61, 93, 102 and 105 were discussed, with claim 54 generally discussed as an independent claim. All statements herein are made in good faith.

During the two interviews, Mrs. Neymeyer-Tynkov indicated that recent Amendments appeared to further prosecution of this application, and that she requested the interview to determine whether any further actions may be taken to facilitate allowance of the application.

Examiner Hissong indicated a continuing concern with the terms "derived from", "derivative" and "derivatives" occurring in claims 93, 102 and 105, as mentioned in the Office Action issued October 27, 2009, paragraph 3 of the rejection under 35 U.S.C. 112. Mrs. Neymeyer-Tynkov agreed on behalf of the Applicant to cancel claims 93, 102 and 105 to facilitate prosecution of the application. No further concerns were indicated with regard to the remaining rejections under 35 U.S.C. 112. The Examiners indicated that claims 55 and 61 need not be canceled. According to Mrs. Neymeyer-Tynkov's understanding, cancelation of claims 93, 102 and 105 will overcome all pending rejections under 35 U.S.C. 112.

With regard to the pending rejections under 35 U.S.C. 103, and in response to questions posed by the Examiners, Mrs. Neymeyer-Tynkov reiterated the general thrust of arguments made in the February 15, 2010 Amendment. The Examiners requested clarification of comments relating to differences in bile salts used in U.S. Patent Number 5,653,987 ("Modi") and Cevc et al., Biochim. Biophys. Acta 1368:201-215 (1998) (hereafter "Cevc"). Mrs. Neymeyer-Tynkov advised that while the same bile salts could be used in Modi's and Cevc's formulations, the bile salts in Modi were added to enhance absorption and would act directly on a barrier to which they were applied. In contrast, bile salts in Cevc were incorporated into transfersomes and, as expressly mentioned in Cevc, did not act like typical bile salts used as absorption enhancers (as in Modi's formulation).

The Examiners also inquired whether the preparation of Modi's compositions would result in the preparation of Cevc's transfersomes or penetrants of the present claims. Mrs. Neymeyer-Tynkov advised that, according to her understanding, the preparation of Modi's compositions would not result in the preparation of Cevc's transfersomes or the presently claimed penetrants. Modi's compositions are made by mixing absorption enhancers in a manner that would not prepare transfersomes/penetrants. Cevc's transfersomes were prepared for instance with additional manipulations, using sonication and other procedures to properly prepare the transfersomes. According to Mrs. Neymeyer-Tynkov's understanding, upon Applicant's submission that the preparation of Modi's compositions did not include preparing penetrants of the present claims, to the Examiners' satisfaction, the pending rejections under 35 U.S.C. 103 will be considered as overcome.

At the end of the interview, there was some discussion as to whether double-spacing the claims would facilitate processing of the application for allowance. Mrs. Neymeyer-Tynkov indicated she would double-space the claims, in case such may be helpful.

Applicant and Applicant's representative thank Examiners Hissong and Nickol for their time and effort in discussing the application. The Examiners are invited to contact Mrs. Neymeyer-Tynkov by telephone with any comments or questions.

REMARKS/ARGUMENTS

In the Claims

No new matter is believed to be added by this Amendment. Claims 93, 102 and 105 are canceled herein, in keeping with discussion detailed in the above Interview Summary. The terms "derived from", "derivative" and "derivatives" no longer occur in the pending claims. Applicant notes that Applicant's cancelation of these claims is to further prosecution, and is intended without prejudice.

The claims have been double-spaced herein, in case such will be helpful in facilitating prosecution of the application.

A few claim amendments made to claims 54, 76, 99, 100, and 110 in an Amendment filed July 13, 2009 in this application were inadvertently omitted from the Amendment filed February 15, 2010 in this application. As the claims were indicated as previously presented in the February 15, 2010 Amendment, the correct text is included herein without further marking.

Regarding rejections raised under 35 U.S.C. 112 in the Office Action issued October 27, 2009:

In view of the cancelation of claims 93, 102 and 105 herein, and the discussion of rejections under 35 U.S.C. 112 in the above Interview Summary, Applicant respectfully submits that all pending rejections under 35 U.S.C. 112 are overcome.

Regarding rejections raised under 35 U.S.C. 103 in the Office Action issued October 27, 2009:

In the above Interview Summary, Applicant notes that during a discussion of the pending rejections under 35 USC 103 in view of Modi (US 5,653,987), it was agreed that upon Applicant's written submission that preparation of Modi's compositions would not include preparing penetrants of the present claims, to the Examiner's satisfaction, pending rejections under 35 USC 103 may be considered as overcome.

Accordingly, herein, Applicant respectfully submits that preparation of Modi's compositions would not include preparing penetrants of the present claims, and requests withdrawal of the pending rejections under 35 USC 103. Applicant notes that the discussion herein is not meant to indicate that the pending claims need be amended in any way, and points out that none of the present claims is directed to a method of preparing a penetrant of the present invention.

A. Specific compositions described and prepared in Modi

Modi discloses the preparation of 5 specific compositions. The compositions are disclosed in Modi Examples I-V, along with their effects on blood glucose level when administered by gavage in rats. As discussed below, Modi's compositions would not prepare the present penetrants at least because (1) compositions disclosed in Modi Examples I-IV were prepared with starting materials that would not prepare the present penetrants; (2) Modi's manner of preparing the composition disclosed in Modi Example V would not prepare penetrants of the present claims; and (3) Modi Example Compositions I,

III, and IV provide blood glucose decreases similar to the composition of Modi Example V, showing that all of the compositions are likely acting as absorption enhancer, not penetrant, compositions.

1. Compositions of Modi Examples I-IV do not include lipids required to make penetrants of the present claims.

As the Examiner may recall, all of the present claims are directed in part to a method for administering a pharmaceutical composition comprising an active ingredient and a carrier comprising a penetrant, the penetrant comprising a minute fluid droplet surrounded by a coating of at least one layer of at least two substances, the substances differing by at least a factor of 10 in solubility in an aqueous medium, wherein the less soluble substance is a lipid and the more soluble substance is a surfactant or more soluble form of the lipid. Lipids according to the present invention are described for instance at pages 26-27 of the application as filed; surfactants are described at pages 27-28 of the application as filed.

The composition described in Modi Example I includes chenodeoxycholate, deoxycholate and polyoxyethylene 9-lauryl ether. When considering whether these substances may, combined together, prepare penetrants of the present claims, Applicant considered which of these substances may serve as a lipid and which as a surfactant of the present claims. Applicant notes that each substance may work as a surfactant according to the present application (see for instance page 27 lines 19-22 and 30-34 of the application as filed), but not as a lipid.

As the starting materials of Modi Example I do not include both a lipid and surfactant of the present claims, Applicant respectfully submits that a composition prepared according to Modi Example I would not include a penetrant of the present claims.

Similarly, absorption enhancers included in Modi Examples II, III and IV include substances that are surfactants but not lipids according to the present invention: Modi Examples II, III and IV include substances such as sodium cholate, oleic acid, linoleic acid, sodium lauryl sulfate, Tween-80 polyoxyethylene sorbitan ester, sodium EDTA, and sodium salicylate. These substances may be surfactants according to the present invention, for instance as indicated at page 27 lines 19-34 of the application as filed. As the preparation of compositions detailed in Modi Examples II-IV includes only surfactants and not lipids according to the present invention, Applicant respectfully submits that preparation of such compositions would not prepare a penetrant of the present claims. Applicant also notes that other substances mentioned in the preparation of compositions of Modi Examples II-IV would not serve as lipids of the present invention.

2. The preparation of the Modi composition disclosed in Example V is different from the preparation of the present penetrants.

The composition prepared in Modi Example V ("Modi Composition V") includes monoolein, which may be considered as a lipid, and deoxycholate and polyoxyethylene 9-lauryl ether, which are surfactants according to the present invention. As penetrants of the pending claims require the presence of a lipid and more soluble surfactant, Modi Composition V may satisfy such requirement. However, the preparation of Modi Composition V would not include preparing penetrants of the present invention, as discussed below.

The preparation of penetrants of the present invention requires the combination of lipids and surfactants. A penetrant of the present invention includes a lipid-surfactant coating surrounding a droplet, too big to permeate (diffuse) through barriers, but capable of crossing a barrier due to its ability to deform to the size or shape of a pore in the barrier. This deformability comes from unusually high local vesicle curvature which can develop at sites of transient, local membrane destabilization without compromising overall aggregate integrity. Lipids alone may make a vesicle such as a liposome that is too rigid to serve the purpose of drug transfer across a barrier; surfactants combined with lipids can soften the vesicle enough to become the deformable penetrants of the present claims. Too little surfactant will not soften the vesicle enough; too much surfactant may solubilise the lipid, causing vesicle instability and dissociation. A basic principle in preparing penetrants of the present invention is, the higher the surfactant concentration, the more adaptable the penetrant, up to the surfactant concentration at which the membrane becomes unstable. (See for instance page 15 line 7 to page 16 line 23, page 17 lines 7-14, page 28 lines 25-34 and pages 40-42 of the application as filed).

Applicant respectfully points out the below table, representing the amount of lipid and surfactant used in Examples of the present application (Appln.) to prepare penetrants of the present invention and mixed lipid micelles (lipid-surfactant combinations having a surfactant concentration sufficient to solubilize associated lipids – see e.g. page 41 lines 11-17 of the present application), as well as amounts of lipid and surfactant used to prepare transfersomes in Cevc (BBA 1368:201-215 (1998)) and absorption enhancer Modi Composition V.

Composition	Amount of lipids and surfactants	Penetrant or transfersome?	Lipid:Surfactant molar ratio[8]
Appln. Exs. 6-9	87.4 mg SPC[3] 12.6 mg cholic acid[2]	YES – penetrant	L:S = 3.7:1
Appln. Exs. 12-13	86.6 mg SPC 13.4 mg NaChol[3]	YES - penetrant	L:S = 3.7:1
Appln. Exs. 30-35	86.3 mg SPC 13.7 mg NaChol	YES – penetrant	L:S =3.7:1
Appln. Exs. 22-29	89.3 mg SPC 10.7 mg NaChol	YES – penetrant	L:S = 4.6:1
Appln. Exs. 22-29	65 mg SPC 35 mg NaChol	NO – mixed lipid micelles	L:S =1:1
Appln. Exs. 22-29	31.6 mg SPC 68.5 mg NaChol	NO – mixed lipid micelles	**L:S = 0.25:1**
Cevc, S. 2.4	8.7 wt% SPC 1.3 wt% NaChol	YES – transfersome	L:S = 3.7:1
Cevc, S. 2.5	88 mg SPC 12 mg NaChol	YES – transfersome	L:S = 3.7:1
Cevc, S. 2.5	44 mg SPC 13.3 mg NaChol	YES – transfersome	L:S = 2:1
Appln. Exs. 14-19	37.7 mg SPC 62.3 mg Tween 80[4]	YES – penetrant	L:S = 1:1
Appln. Exs. 22-29	64.5 mg SPC 35.5 mg Tween 80	YES – penetrant	L:S = 3.1:1
Appln. Exs. 20-21	14.8 mg SPC 85.2 mg Tween 80	NO – mixed lipid micelles	**L:S = 0.29:1**

Appln. Exs. 22-29	13.2 mg SPC 86.8 mg Tween 80	NO – mixed lipid micelles	**L:S = 0.26:1**
Appln. Exs. 22-29	7 mg SPC 93 mg Tween 80	NO – mixed lipid micelles	**L:S = 0.13:1**
Modi Composition V	0.1g monoolein[5] 0.25g deoxycholate[6] 0.25 g polyoxy-ethylene 9-lauryl ether[7]	- - -	**L:S = 0.27:1**

1 SPC = soybean phosphatidylcholine – estimated average molecular weight (MW): 776 (Sigma Product Information, Product Number P7443)
2 Cholic acid, MW = 408.6 (Sigma-Aldrich Product Number 27010)
3 NaChol – sodium cholate. MW = 430.6 (Thomas Scientific)
4 Tween-80, estimated average molecular weight = 1310 (Sigma Product Information, Product Number P8074)
5 Monoolein, MW=356.54 (Chemical Abstracts)
6 Sodium deoxycholate, MW=414.561 (Chemical Abstracts)
7 Polyoxyethylene 9-lauryl ether, MW=582.81 (Chemical Abstracts)
8 Calculation of lipid:surfactant molar ratio: (Amount of lipid substance / lipid MW) / (Amount of surfactant substance / surfactant MW)

As may be seen in the above table, most penetrants of Examples of the present invention and transfersomes of Cevc were prepared with a lipid to surfactant molar ratio of about 4:1 when made with sodium cholate (in Cevc Section 2.5, a transfersome composition was reportedly prepared with a 2:1 L:S ratio) and 3:1 or 1:1 when made with Tween-80. Mixed lipid micelles of the present Examples were prepared in a lipid:surfactant molar ratio range of 1:1 or 0.25:1 with sodium cholate and about 0.3:1 to 0.1:1 with Tween-80. Overall, penetrants of the present invention tend to include high amounts of lipid relative to amounts of surfactant, and mixed lipid micelles tend to include high amounts of surfactant relative to amounts of lipid. Penetrants and mixed lipid micelles of the present application were both made at a 1:1 L:S molar ratio with different starting materials, however, no penetrants were disclosed as prepared where the ratio of surfactant molecules was 3-4 times greater than lipid molecules.

The lipid: surfactant molar ratio of Modi Composition V is 0.27:1, meaning that about 4 surfactant molecules are present for every 1 lipid molecule. This ratio falls within the lipid:surfactant ratio range of mixed lipid micelle formulations made with both sodium cholate and Tween-80 in the present application (shown in bolded text in the table above). Applicant recognizes that Modi Composition V is made with different surfactants and lipids than the present Examples, and that different lipid-surfactant combinations may require different molar ratios to prepare penetrants of the present invention. However, the comparison of lipid:surfactant molar ratio of Modi Composition V with the present Examples clearly shows that Modi Composition V includes a much greater ratio of surfactant molecules than lipid, similar to the preparation of conventional mixed lipid micelles expressly described in the present application, not penetrants.

This difference is underscored by differences in the simple preparation method used for Modi Composition V and additional processing used to prepare penetrants and transfersomes. Modi discloses rapidly stirring 0.1 g monoolein, 0.25 g deoxycholate and 0.25 g POE 9-lauryl ether in cold distilled water (4°C) to dissolve. (See e.g. Modi column 4 line 61 to column 5 line 5 and column 7 lines 39-60, as well as all other Modi Examples for preparation of other Modi compositions). In contrast, pages 40-42 of the present application describe, in conjunction with PCT/EP98/006750 (see page 13 lines 21-26 and page

42-lines 6-7 of the present application), processing including lengthy room temperature stirring processes, multiple freeze-thaw and filtration steps to contribute to the stability of the penetrants and extrusions to manipulate penetrant size as desired (see also e.g. the present application page 14 lines 8-10 and PCT/EP98/006750 pages 29-34). Page 13 lines 21-26 of the present application also indicates that documents PCT/EP91/01596 and PCT/EP96/04526 may also exemplify formulations of penetrants of the present invention (see U.S. Patent No. 6,165,500 and Publication No. 2002048596, for U.S. patent publications, respectively); all transfersomes prepared in those documents generally included some form of extra processing, such as sonication, freeze-thawing, filtration, dissolution of lipid and surfactant in ethanol with subsequent solvent removal, preparation at temperatures greater than 4°C, etc. Further, Cevc Section 2.4 describes preparing transfersomes by dissolving SPC in ethanol, mixing with sodium cholate, then mixing with triethanolamine-HCl buffer, sonicating, freeze-thawing 2-3 times, and bringing to desired size via ultrasonication or intermediate pressure homogenization. Cevc Section 2.5 also instructs the skilled person to mix insulin with SPC and sodium cholate dissolved in ethanol.

It makes sense that additional processing is used to prepare the present penetrants, in contrast to Modi's simple dissolution of absorption enhancers in water. Modi's higher molar ratio of more water-soluble surfactants to less water-soluble lipids makes it easier to dissolve surfactants and solubilize lipids in aqueous solution. The additional processes used to prepare penetrants of the present claims aid in working with the more lipid-rich penetrants.

Applicant further notes that page 41 lines 11-17 of the present application discloses that mixed lipid micelles are made simply by mixing ingredients similar to those used to make a penetrant in aqueous phase, but in a different ratio, so the surfactant concentration is above the solubilization concentration value. This preparation of mixed lipid micelles is similar to the preparation of Modi Composition V.

Overall, Applicant submits that preparation of penetrants of the present claims may include a variety of techniques to accommodate penetrant lipid content and to facilitate penetrant stability. In contrast, Modi Composition V appears to prepare a more conventional composition such as one including mixed lipid micelles, in view of its high surfactant content and simple aqueous formulation.

For at least the above reasons, Applicant respectfully submits that the preparation of Modi Composition V does not prepare penetrants of the present invention, and requests withdrawal of the pending rejections under 35 USC 103.

Applicant further notes that the preparation of Modi Composition V is clearly and expressly meant to prepare a composition to enhance absorption (diffusion), and not an attempt to prepare penetrants of the present invention. As mentioned above, penetrants of the present claims must include proper ratios of lipids and surfactants, to soften a lipid aggregate without solubilizing or disintegrating it. The accidental preparation of the present penetrants is unlikely where the preparers do not intend to make such penetrants, and do intend to make compositions that will enhance absorption across a barrier.

3. Modi Composition V acts like the state-of-the-art absorption enhancer compositions of Modi Examples I, III and IV.

As indicated in section 1 above, Modi Examples I, III and IV disclose compositions that do not contain proper starting materials and therefore could not make penetrants of the present invention. A

comparison of data acquired after administering absorption enhancer compositions of Modi Examples I, III and IV with data acquired after administering Modi Composition V shows that Modi Composition V provides similar results, and thus acts like, absorption enhancer (non-penetrant) Compositions I, III and IV.

Specifically, Modi Example I Table I shows a decrease in blood glucose levels from on average 28.3 ± 1.2[1] mmol glucose/L (pre-administration) to 8.4 ± 2.0 mmol glucose/L (2 hours after administration). Similarly, 2 hours after administration, Example III Table IV shows a decrease to 10.2 ± 2.1 mmol glucose/L; Example IV Table V, to 11.8 ± 2.5 mmol glucose/L; and Example V Table VI, to 12 ± 2.5 mmol glucose/L. (Modi Example II does not show a decrease in blood glucose after administration, as discussed below). Applicant respectfully submits that this simple analysis of Modi Examples I, III, IV and V, and Tables included therein, shows that each of Modi's compositions achieved a similar reduction in blood glucose 2 hours after administration.

The similar results achieved by Modi Compositions I, III, IV and V further indicate that the compositions employed a similar mechanism of action. As Modi Examples I, III and IV could not decrease blood glucose levels via penetrant activity of the present invention, and as Modi Composition V showed a decrease similar to that of Modi Examples I, III and IV, it appears that Modi Composition V also worked without penetrants to decrease blood glucose levels.

With regard to Modi Example II, Modi discloses that the composition prepared in Example II does not lower blood glucose because it does not include at least 2 of the absorption enhancers Modi indicates as critical to success for its formulations. (2 hours after administration, Modi Example II Table III indicates a blood glucose level of 24 ± 3.2 mmol glucose/L in comparison with 28.8 ± 0.7 mmol glucose/L preadministration). See e.g. Modi column 2 lines 12-28 and Example II column 6 lines 24-54. Modi discloses including Example II for comparative purposes, to show that a "formulation which contains only one absorption enhancer ... has very little metabolic effect on the blood glucose levels." As indicated above, Modi composition II does not satisfy basic requirements of a lipid and surfactant and therefore could not make a penetrant of the present invention.

Applicant also respectfully notes that Modi Example II uses only 40-50% of the amount of total absorption enhancer of Examples I, III, IV and V (0.3 g sodium cholate in Example II v. 0.6-0.85g combined absorption enhancer in the other Examples; same final volume). The skilled person, noticing this, may consider whether the amount of absorption enhancer used in Modi Example II is simply insufficient to obtain an effect on blood glucose, rather than a lack of a combination of absorption enhancers. While Modi expressly discloses the need for 2 absorption enhancers for its formulations to work, Comparative Example II does not appear to definitely confirm this.

B. Modi's description of potential combinations of substances

Modi generally discloses compositions that include an active ingredient and at least two absorption enhancing compounds, listing 20-30+ absorption enhancers including sodium deoxycholate, Tween 80, phosphatidylcholine and phosphatidylethanolamine (see e.g. Modi column 2 lines 12-65, column 3 lines 1-4). First, Applicant notes that Modi does not distinguish between substances that may serve as lipids or surfactants in its formulations, but rather indicates that any combination of its defined group of permeation enhancers will work. Second, as discussed above, Applicant respectfully notes that

[1] Standard deviation, as calculated by MS eXcel spreadsheet STDEV function.

even if Modi inadvertently combined substances that may make penetrants of the present invention, Modi teaches the skilled person to use high concentrations of substances that may be surfactants of the present invention and relatively small amounts of lipid, as in Modi Composition V, and thus would not be taught to prepare a penetrant of the present invention.

At least in view of the foregoing discussion, Applicant respectfully submits that all pending rejections under 35 U.S.C. 103 are overcome.

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Applicant respectfully requests allowance of the above-identified application. In the event that the Examiner has any questions or concerns regarding this Amendment, or any further concerns regarding allowing this application, the Examiner is invited to contact the below-signed representative by telephone to discuss.

Respectfully submitted,

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Date

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